GENERAL REVIEW

UDC: 616.1-089
DOI: 10.2298/VSP140515079L

Structural features of arterial grafts important for surgical myocardial revascularization: Part I – Histology of the internal thoracic artery

Strukturne karakteristike arterijskih graftova značajnih za hiruršku revaskularizaciju miokarda: Deo I – Histologija unutrašnje torakalne arterije

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Key words:
myocardial revascularization; vascular patency; mammary arteries; histology.

Ključne reči:
miokard, revaskularizacija; vaskularni graft, prolaznost; aa. mammariae; histologija.

Introduction

In contemporary heart surgery the following arterial grafts are used: the internal thoracic artery – ITA (*arteria thoracica interna*), the radial artery, the inferior epigastric artery and the right gastroepiploic artery. Favorable features of arterial grafts in surgical revascularization of the myocardium are: uniform size of arterial grafts and diameter which corresponds to the diameter of coronary blood vessels, technical and topographical accessibility, the fact that they do not contain valves, that they are as well adapted to arterial flow and pressure, and, in case of the ITA adaptation to intrathoracic respiratory changes of pressure [1–4]. Arterial graft of the ITA, is one of the most frequently used grafts in surgical revascularization of the myocardium, besides the venous graft of the great saphenous vein, (*vena safena magna*).

Arterial grafts are introduced into surgical practice because of the need to establish efficient system for multiple revascularization of the myocardium, and the peak in their implementation is reached by introducing modern techniques of composite or creative grafts. This contemporary approach implies complete revascularization of myocardium using arterial grafts. At the same time, the left internal thoracic artery is used for revascularization of the left anterior descending coronary artery, while composite graft of the right gastroepiploic artery anastomosed with the radial artery is used for the revascularization of the right coronary artery and the left circumflex artery [5]. The inferior epigastric artery or the right internal thoracic artery can be used instead of the radial artery in this composite fashion.

Indications for using composite arterial grafts are a very small diameter or a high degree of stenosis of target coronary blood vessels, the need for multiple revascularizations with more than three distal anastomosis and avoiding bilateral dissection of internal thoracic artery in diabetic patients [6].

Histology of the internal thoracic artery

Features of the ITA, as almost ideal graft, are determined with its specific histological structure. According to the original definition, it is the only peripheral artery of elastic type in human organism, with well formed internal elastic membrane [7]. However, in modern research it was shown that the internal thoracic artery is an artery of the transitional or mixed type [8] (Figures 1A–H).

The wall of the ITA is composed of three layers: *tunica intima, tunica media* and *tunica adventitia* (Figure 1D). *Tunica intima* has a typical structure and contains endothelium

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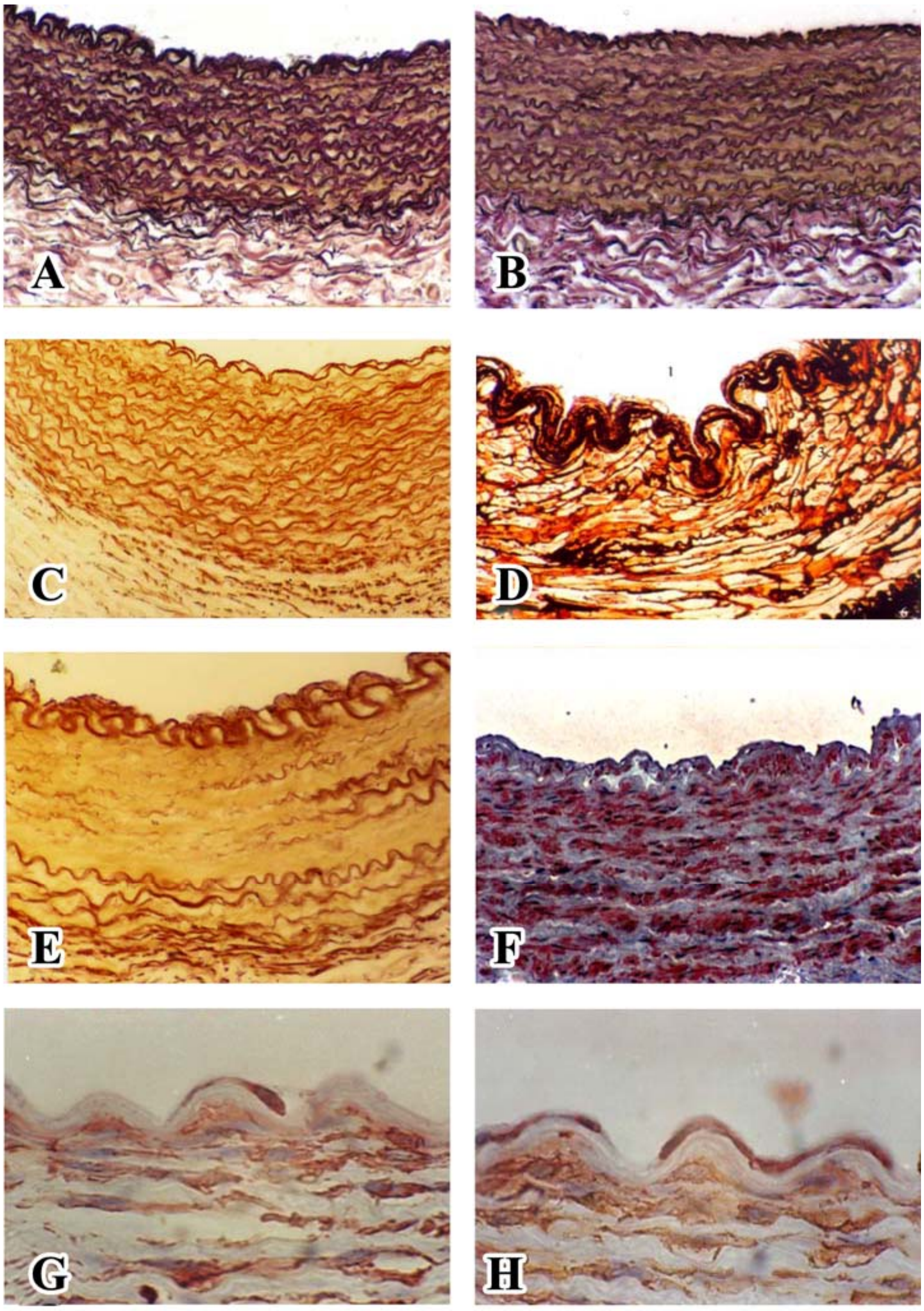

Fig. 1 – The internal thoracic artery: (A, B, C and E) Weigert van Gieson staining for elastic fibers; (D) methenamine silver staining; (F) immunohistochemical staining for alpha smooth muscle (α SMA) (EnVision/AEC); (G and H) immunohistochemical staining for alpha smooth muscle (α SMA) (LSAB+/HRP/DAB) [original magnification: (A) 32×; (B, C, E and F) 64×; (D) 100×; (G and H) 256×]
A and B: artery of mixed (transitional) type, with inner (muscular) layer and outer layer with elastic lamellae; C: segments with elastic phenotype; D: 1. arterial lumen; 2. *tunica intima* and the internal elastic lamina; 3. *tunica media*; 4. elastic lamellae; 5. smooth muscle cells; 6. *tunica adventitia*; E: segments with muscular phenotype and small number of elastic lamellae; F: circular arrangement of smooth muscle cells in the inner layer of the tunica media and spiral arrangement of smooth muscle cells in the outer layer of the tunica media; G and H: smooth muscle cells are present in the subendothelial connective tissue in infant (2 months of age).

and poorly developed layer of subendothelial connective tissue. Thickness of the intima is very small, around 2.5 μm in the thinnest segments, and the mean values of intimal thickness vary between 9 μm, in persons younger than 40 years, and 20 μm, in persons older than 60 years [8, 9].

Molecular, cytological and histological features of the ITA endothelium and the composition of subendothelial connective tissue are important for low level of atherosclerosis. The endothelium of the ITA is an important subject of intensive research. It has been shown that preserving the endothelium is a priority during surgical preparation of the grafts, because the ITA contains a potent system of endogenous nitrate which prevents vasospasm, thrombus formation and occlusion of the graft [10, 11].

Paracrine function of the endothelium is one of the crucial factors responsible for notable differences in the long-term patency of venous and arterial grafts. The level of nitric oxide (NO), which is produced by endothelium of the ITA, is dramatically higher in comparison to low and variable amount of NO secreted by endothelium of the great saphenous vein [12–15]. Generally taken, basal production of NO is higher in arterial than in venous circulation [16, 17], while venous vessels show larger sensitivity to endothelin-1 in comparison to arterial vessels [18].

Intensive release of NO is also typical for vascular endothelium of the ITA branches. Studies have shown that perforating branches of this artery, which provide vascularisation of upper inner quadrant of the breast, have striking ability of endothelium dependent vasodilatation completely induced by nitrogen monoxide (NO or endothelium-derived relaxing factor – EDRF), which is important for perfusion of glandular tissue adequate to changeable physiological requirements during breastfeeding and lactation [19]. This feature, with optimal diameter, makes the ITA an ideal recipient blood vessel for free tissue transfers in thoracic region, especially during breast reconstruction [20].

Reasons for venous grafts insufficiency in comparison to arterial grafts are weaker activity of antioxidant enzyme, superoxide dismutase, larger retention of low-density lipoproteins (LDL) in venous vesseles [21], and as well the fact that several growth factors, such as platelet-derived growth factor (PDGF), stimulate proliferation and migration of smooth muscle cells of the great saphenous vein, but not of the internal thoracic artery [22]. Larger retention of LDL in venous grafts is initiated by larger amount of sulfated glycosaminoglycans in the subendothelial connective tissue of the venous vessels in comparison to arterial vessels. Also, after the implantation of the venous grafts the deposition of sulfated glycosaminoglycans increase, making the venous grafts more permeable and susceptible to lipid retention [21].

The preserved endothelium and its anti-thrombogenic function, as well as the absence of aggregation and activation of platelets due to low level secretion of platelet-activating factor and platelet-activating factor acetylhydrolase, are also designated as causes of delayed atherosclerosis of the internal thoracic artery [23]. The internal thoracic artery endothelium contains more anti-thrombotic molecules as, for example, heparin sulfate and tissue plasminogen activator [24].

Besides, endothelium of the ITA is proved to have fewer fenestrations, lower permeability of intercellular junction and low level of intercellular adhesion molecule-1 (ICAM-1) with lower potential for adhesion, rolling and transmigration of inflammatory cells [24, 25]. This is in concordance with basically lower level of inflammation in the atherosclerotic lesions of the internal thoracic artery [8].

All these factors contribute to low level atherosclerosis and to the superior patency rate of the ITA when used as the coronary artery by-pass graft (CABG).

Low grade atherosclerosis is an unique feature of the ITA. According to many researchers, the ITA rarely develops atherosclerotic lesions. In a comprehensive pathoanatomical study, which included 3,409 specimens of the ITA, 97.5% of them were macroscopically unaltered. Only in six of the arteries, developed atherosclerotic plaques were shown, and 78 arteries have shown atherosclerotic lesions of lower degree [26]. Other similar studies proved that up to 87% of arteries were free of atherosclerosis and that only 3.1% had stenosis on the branching point where the ITA derives from the subclavian artery [27, 28]. According to our research, frequency of atherosclerotic lesions increases with aging. Atherosclerotic lesions type IV occur in 1% of patients younger than 40 years and in 7.6% of patients older than 60 years [9].

However, the ITA is not resistant to the development of intimal hyperplasia with aging [8, 9, 29, 30]. In most of the patients, intimal thickening of the internal thoracic artery develops primarily because of intimal hyperplasia. It is also known that smooth muscle cells in the internal layer (*tunica intima*) of this artery can already be found in the first few years of life [9, 31–33] (Figures 1G–H).

Besides that, it was shown that known risk factors for the development of atherosclerosis: hypercholesterolemia, diabetes mellitus, male gender, smoking and hypertension stimulate intimal hyperplasia and the development of ITA atherosclerosis [8, 9, 34–36].

Specific structural features of the tunica media of the ITA

The *tunica media* of the ITA is composed of two layers: inner, which is made up of several layers of circularly oriented smooth muscle cells, and outer, with a variable number of elastic lamellae and spirally arranged smooth muscle cells in interlamellar units (Figure 1F). Such a structure completely corresponds to the well-known definition of arteries of mixed type and contemporary classification of arteries [37].

In the outer layer of the tunica media, the number of elastic laminae, which are different from internal and external elastic membranes, varies depending on an arterial segment.

van Son et al. [7], who first described histology of the ITA, paid great attention to the appearance of the *tunica media* and the number of elastic lamellae. The first centimeter of the artery after the take off from the subclavian artery (*a. subclavia*) had characteristics of elastic artery with 8–18 elastic lamellae.

In the further course of the artery, four different types of the *tunica media* of the ITA can be distinguished: elastic, which, together with the internal and the external elastic membranes; contains between 8 and 18 well-developed; densely arranged elastic lamellae with moderate number of smooth muscle cells (Figure 1C); elastic-muscular, with five to seven concentric, elastic lamellae and slightly larger number of smooth muscle cells in comparison to the previous type (Figures 1A–B); muscular type, with the domination of smooth muscle cells and three to four poorly formed elastic lamellae, including the internal and the external elastic membrane (Figure 1E); muscular type, which consists almost exclusively of smooth muscle cells with sparse single elastic fibers distributed between muscle cells and without well developed elastic lamellae [7].

However, new studies have shown that, in general, the number of elastic laminae of the ITA progressively decreases from the initial portion to the terminal branches, which is in accordance with its topographical localization and histological structure of transitional artery, inserted between classically structured elastic artery (subclavian artery) and typical muscle arteries (superior epigastric artery and musculophrenic artery) [29] and represents phenomenon which has been observed in the previous research on the number of elastic lamellae in the aorta and the ITA [7, 38–40]. The number of elastic lamellae in the outer media shows conspicuous individual variations [8, 9, 29].

This kind of morphological finding is particularly significant from the functional point of view. The research shows that transitional arteries, due to their specific structure, are capable of adapting to altered hemodynamic conditions and for vascular remodeling during life, in accordance with the changed functional requirements [41, 42]. Similarly to elastic arteries, the presence of elastic lamellae allows these arteries to maintain a constant blood flow even during diastole by passive contraction. On the other hand, the presence of well-defined muscular layer creates conditions for a wide degree of physiological adaptability of the ITA that is vasospasm in conditions of low flow and an increase in the diameter at increased blood flow, which is extremely important in terms of graft performance. It has been shown that the use of the ITA, even in conditions of low free flow gives good results, because this graft has a high ability to adapt to changing hemodynamic conditions, and if there is no damage to the graft during mobilization, the blood flow can significantly increase following the increased demands of the myocardium [11].

The extracellular matrix of arterial grafts media contains a developed network of collagen type IV. Collagen type IV and laminin stabilize the extracellular matrix of blood vessels, inhibit the activity of matrix metalloproteinases, delay the transformation of vascular smooth muscle cells from contractile to synthetic phenotype as well as their proliferation and migration. These effects of collagen type IV and laminin are opposite to the effects provoked by fibronectin [43–45].

The internal thoracic artery and the positive remodeling

Another important aspect is the fact that the media of the ITA gradually thickens with age and with the development of intimal hyperplasia [8, 9]. Also, this happens during the development of early atherosclerotic lesions types. It was, also, shown that chronic increase in blood flow leads to the increase of the ITA diameter [46, 47]. These facts pointed towards the capability of the ITA for positive remodeling. The ability for positive remodeling probably contributes to the absence of complications after CABG surgery, namely *angina pectoris* and myocardial infarction.

The mean values of the media thickness range between 160 μm and 250 μm [8, 9].

The elastic lamellae features

Between the intima and the media lies a well-developed internal elastic lamina. The thickness of the internal elastic membrane is between 2.0 μm and 2.5 μm, and it is well-formed even at birth and in the first years of life it significantly thickens and contains a small number of fenestrations. This perfectly formed internal elastic membrane represents a specific structure of the ITA and it is especially well-developed in the younger age groups [31]. It was considered that a well formed internal elastic membrane prevents migration of smooth muscle cells from the media to the intima and that it plays a key role in preventing early atherosclerotic changes [31].

However, modern research has shown that perfectly formed internal elastic lamina is not a permanent feature of the ITA. After the age of sixty, there is a sudden decrease in the thickness of the internal elastic membrane, while the number of fenestrations increases significantly from the age of forty, especially in men [29]. This also applies to all elastic lamellas of the ITA, which become thinner with age, and have larger and more numerous fenestrations. Degradation of the elastic skeleton of the internal thoracic artery is particularly well-expressed after the age of sixty. This fact indicates that the process of aging significantly disrupts the integrity of the elastic skeleton of the ITA, and probably makes the artery more vulnerable to the development of intimal hyperplasia and atherosclerosis [29]. Consistent with this finding are conclusions of a study that enclosed 5,601 patients and tested the long-term prognosis of bilateral ITA grafts in patients older than 70 years. There was no clear advantage of bilateral ITA grafting in these patients in comparison to vein grafts or the combination of the ITA and the saphenous vein grafts [48]. Aging limits the superiority of the ITA.

These data are opposite to predominant attitudes from previous studies that claim that parts of the ITA with many elastic lamellae have lower level of hyperplasia than the intima or atherosclerosis, and that elastic lamellae are perfect and continual protection from the smooth muscle cells migration [7]. Nevertheless, among different media patterns or phenotypes there are no differences in the thickness of the intima or the atherosclerosis grade [8]. The benefits from using proximal parts of the ITA came mainly from their functional adaptability caused by characteristics of mixed arteries [8]. Elastic lamellae are not solely factors that delay atherosclerosis or intimal hyperplasia [8].

Between the media and the adventitia there is a well-formed external elastic membrane.

The issue of vascular wall resident progenitor cells in the adventitia of the internal thoracic artery

Tunica adventitia of the ITA contains a wide network of connective tissue composed of longitudinally arranged elastic and collagen fibers. Its thickness is about 100 μm [7]. Thickness of the adventitia in some segments is equal to the thickness of the media, which is also similar to the muscular type arteries, rather than elastic arteries [8, 9]. A particularly important feature is the presence of numerous CD34 immunoreactive cells, which are considered as resident progenitor cells of the vascular wall (vascular wall resident progenitor cells) that are very abundant in the adventitia of the internal thoracic artery [9, 49]. It is believed that these cells have the potential to differentiate to endothelial cells, smooth muscle cells, and endothelial cells of *vasa vasorum*. Also, the endothelium of the ITA artery contains many CD34 immunoreactive cells. This feature is retained by the endothelium in the aging process, as well as during the development of atherosclerosis, which is opposite to the coronary arteries, the radial artery and the gastroepiploic artery. It is believed that the presence of CD34 immunoreactive cells indicates the regeneration potential, which is continuously maintained, and may explain the low tendency of this artery for the development of atherosclerosis [9].

The wall thickness of the internal thoracic artery and the implication for surgical use

The mean value of the wall thickness of the ITA varies between 240 μm and 360 μm in the different age-related groups with the mean value of 282.79 ± 93.54 μm [8, 9]. This provides nutrition of the wall of the ITA from the lumen of the artery, which was confirmed by immunohistochemical and electron microscopic studies [10]. Specifically, it has been found that the nutritional needs of the artery with a wall thickness of less than 350 μm and with less than 29 lamellar units of media, are provided by the diffusion process from the blood flowing through the artery, and the 29th lamellar layer and 350th μm represent a topographic limit to which it is possible to conduct the process of diffusion. All the other lamellar units of these types of arteries settle their nutritional needs thanks to the presence of *vasa vasorum* [50, 51]. Therefore, the removal of adventitial layer of the artery during graft skeletonization does not impair the ultrastructure of the artery, so integrity of the endothelial cells and their connections and adherences to the basement membrane are preserved, regardless of the aggressiveness of the surgical approach [10]. From the perspective of modern cardiac surgery practice, this histological finding has important implications, because it suggests a certain amount of freedom in the surgical preparation of the graft, as well as the possibility to use the artery as a free, skeletonized or a composite graft without the risk of ischemic damage to the arterial wall [7, 52]. Lymphatic drainage of the wall of the internal thoracic artery is very effective, in contrast to the coronary arteries, which is why this is also considered as a possible cause of delayed development of atherosclerotic changes [7].

Diameter of the internal thoracic artery

The diameter of the internal thoracic artery varies between 1.9 and 2.6 mm [24]. The diameter of the internal thoracic artery is almost ideally suited to the diameter of the left anterior descendening coronary artery. The lack of discrepancy in the caliber of blood vessel combined with a good surgical technique minimizes the occurrence of turbulent flow and thrombosis at the anastomotic site [53].

Gender specific differences

The media of the male patients is significantly larger than the media of female patients and the male gender is an independent predictor factor for the internal elastic membrane disruption during ageing [8]. On the other hand, there is a reduced level of NO and endothelial nitric oxide synthase (eNOS) in the endothelium of the internal thoracic arteries of the post-menopausal women with poor outcome expectance in CABG patients [54].

Left-to-right specific differences

In terms of morphometric parameters there is no difference between the arteries on the left and the right side of the body, a finding that is particularly important from the point of view of numerous studies that determine the efficiency of bilateral internal thoracic artery graft, and the applicability of the right internal thoracic artery grafts within composite graft systems and multiple arterial revascularization systems [8, 55–57].

Angiographic comparision of the left internal thoracic artery (LITA) graft to the nonharvested right ITA in the same patient indicated that the diameters of the LITA were significantly smaller, while the intima thickness, the maximal intimal thickness and the intima-media ratio were significantly larger in the LITA. NO mediated vasodilatation was not different between the left and right arteries [58].

Use in the surgical myocardial revascularization

Due to anatomical features, the most commonly used artery is the left internal thoracic artery, as a direct coronary artery by-pass graft to the left anterior descending, diagonal or marginal branch of the circumflex coronary artery [4, 35]. The right ITA is used as a free graft for anastomosis with the marginal branch of the circumflex coronary artery [56, 59, 60].

A 30-year long surgical practice in the use of this graft, as well as numerous comparative arteriographic, clinical and histopathological studies have clearly demonstrated the superiority of this arterial graft. The monitoring of the patients during the period of 11 to 18 months after coronary artery bypass surgery performed with the ITA graft, determined the rate of graft patency of 89.8% to 100% [61, 62]. During the 10-year postoperative period, this parameter has a value of more than 80% with the development of low level atherosclerotic changes [63, 64]. For example, during the same period, the rate of graft patency of saphenous vein is between 41% and 56% [7, 65, 66]. In addition, in all of the implanted vein grafts, within six months to one year, a diffuse thickening of the intima develops with the accumulation of foam cells along the lumen of the blood vessel, which indicates an unstable morphology of these lesions and a poor prognostic impact on the fate of these grafts [67].

Following a period of 10 years after surgical myocardial revascularization it was found that patients with great saphenous vein graft compared to patients with implanted internal thoracic artery graft have a 1.41 times greater risk of developing late myocardial infarction, 1.25 to 1.27 times greater risk to develop other late cardiac complications and the need for hospitalization and 2.00 times more likely they will need the reoperation. Finally, the possibility of fatal outcome is 1.61 times higher among patients with venous graft [68].

Contemporary studies proved that the outcome of CABG with ITA is superior to percutaneous coronary interventions (PCI) in terms of outcome, the need for repeated revascularization and mortality rate after 3, 4 and 5 years postoperatively [69, 70] and remains the therapy of choice for multivessel disease [71–75]. Excellent patency rate was observed when the ITA was used in the technique of minimally invasive direct coronary artery bypass grafting (MIDCABG) [71, 72].

Conclusion

The internal thoracic artery is currently the conduit of the first choice in the surgical myocardial revascularization. Its unique histological characteristics and hemodynamic adaptability enable long-term patency and reliable perfusion of ischemic myocardium. The adaptability of the internal thoracic artery comes from the fact that this is the artery of mixed (transitional) type and from the highly active system of endogenous nitrate. The important features from the clinical point of view are low level of atherosclerosis, stable morphology of atherosclerotic lesions and a potential for positive remodeling. The true challenge in future studies should be further research on the capacity for endothelium renewal and the differentiation of vascular wall resident progenitor cells present within the adventitia of the internal thoracic artery.

Acknowledgements

The research activities were supported by the grants No. 175005, 175061, III41002, III45005 and 41022 from the Ministry of Education, Science and Technological Development of the Republic of Serbia.

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Received on May 15, 2014.
Accepted on July 28, 2014.
Online First August, 2015.